UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/230,955	05/04/1999	ROBERT JAMES MASON	A-67653/DCA/	3606

23973 7590 09/09/2003

DRINKER BIDDLE & REATH
ONE LOGAN SQUARE
18TH AND CHERRY STREETS
PHILADELPHIA, PA 19103-6996

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/230,955	MASON ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-5,7 and 10-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *5 and 7* is/are allowed.

6)☐ Claim(s) *1-4 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Please note that the examiner assigned to this application has changed.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. Claims 1, 3 and 4 have been amended. Claim 8 has been canceled. Claims 10-12 have been added. Claims 1-5, 7 and 10-12 are pending and under consideration.

4. The rejection of claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by Porta et al is withdrawn in light of applicants amendments.

5. The rejection of claims 1-4 under 35 U.S.C. 112, first paragraph, as stated in section 10, page 5 of the Office action of Paper no. 10 is withdrawn in light of applicants amendments.

6. Claims 1-4 and 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "panel including at least one monoclonal antibody specific for columnar cells and at least one monoclonal antibody specific for squamous cells....wherein the percentage binding of the at least one monoclonal antibody specific for squamous cells is decreased in premalignant or neoplastic cells with respect to normal cells". However, the claim fails to relate the binding of the at least one monoclonal antibody which specifically binds to columnar cells with the screening for premalignant or neoplastic disease as stated in the method preamble. For purpose of examination, antibodies which specifically bind columnar cells having both a greater and a lesser percentage binding to premalignant or neoplastic cells relative to normal cells will be considered.

Claims 2 and 3 recite the limitation "wherein the percentage binding" of the monoclonal antibodies is decreased with respect to normal cells. It is unclear if the "percentage binding" refers to the number of positive samples within a group of sample, or if "percentage binding"

refers to a decrease in binding to the same cell types or an overall decrease in staining by the antibody. For instance, in Kerr et al (reference C of the IDS filed July 1, 1999), there is reported an MC2 antibody which strongly stains the "broad zone" of suprabasal cells in normal cervical cells, but iCIN, levels I and II exhibit a reduction in the staining of the zone of suprabasal cells, while in CIN level III , only the most superficial of cells stain with the antibody. This is one type of decreased percentage of binding with respect to normal cervical cells. In contrast, Malecha et al (Int Journal of Gynecological Pathology, 1992, Vol. 11, pp. 24-29) reports that the AE8 antibody (Table 1) reacts with 36 out of a total of 36 samples of squamous epithelium, but only 2 out of 7 samples of CIN II. this is another decrease in the percentage binding with respect to normal cervical cells. For purpose of examination both alternatives will all be considered within the metes and bounds of the claims.

7. Claims 1-4 and 10-12 are rejected under 35 U.S.C, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to new matter

Claim 1 is drawn to a method of screening for a premalignant or neoplastic disease state in a cervical smear sample containing cells of the cervix, the method comprising contacting said sample with a panel of two or more monoclonal antibodies wherein said panel binds to surface antigens on normal cells of the cervix in a pattern which represents normality, wherein said panel included at least one monoclonal antibody specific for columnar cells and at least one monoclonal antibody specific for squamous cells, determining the binding of said monoclonal antibodies to said sample and comparing the binding with a pattern of binding in a normal cervical sample, wherein the percentage binding of the at least one monoclonal antibody specific for squamous cells to premalignant or neoplastic cells is decrease relative to normal cells. Claim 2 embodies the method of claim 1 wherein the monoclonal antibodies comprise one or more polypeptide each comprising an antigen binding domain. Claim 4 embodies the method of claim 1 wherein one or more of the monoclonal antibodies comprise a polypeptide able to bind to an antigen which can be bound by one or more antibodies obtained from a hybridoma selected

from the group consisting of the ECAC 95020718 (the 6B5 antibody), 95020716 (the 2C7 antibody), 95020720 (the 9G5 antibody), 95020717 (the HG3 antibody) and 95020719 (the BC4 antibody). Claim 10 embodies the method of claim 1 wherein said panel of monoclonal antibodies comprises a monoclonal antibody having an antigen binding domain obtained from the hybridoma of ECACC 95020716 (the 2C7 antibody).

Claim 3 is drawn to a method of determining a premalignant or neoplastic disease state in a cervical smear sample comprising contacting a panel or two or more monoclonal antibodies with said sample and comparing the binding of said monoclonal antibodies in said sample with the binding to a normal cervical sample wherein the percentage binding of the two monoclonal antibodies to premalignant or neoplastic cells is decreased with respect to normal cells and wherein the panel comprises one or more polypeptide comprising an antigen binding domain obtained from a hybridoma selected from the group consisting of ECAC 95020718 (the 6B5 antibody), 95020716 (the 2C7 antibody), 95020720 (the 9G5 antibody), 95020717 (the HG3 antibody) and 95020719 (the BC4 antibody). Claim 12 embodies the method of claim 3 wherein said panel of monoclonal antibodies comprises a monoclonal antibody having an antigen binding domain obtainable from the hybridoma of ECACC 95020716 (the 2C7 antibody).

Applicant has amended the claim 1 to incorporate the limitations "wherein said panel binds to surface antigens on normal cells of the cervix in a pattern which represents normality, said panel including at least one monoclonal antibody specific for columnar cells and at least one monoclonal antibody specific for squamous cells" and "wherein the percentage binding of the at least one monoclonal antibody specific for squamous cells to premalignant or neoplastic cells is decreased with respect to normal cells". Applicant has amended claim 3 to recite the limitation "wherein the percentage binding of the two or more monoclonal antibodies to premalignant or neoplastic cells is decreased with respect to normal cells". Applicant refers to pages and lines of the specification as support for the amendment of at least one antibody which binds to squamous cells and at least one antibody which binds to columnar cells, wherein the percentage of binding to squamous cells in a premalignant of neoplastic sample is decreased with respect to a normal sample of cervical cells. These have been carefully considered but found lacking in support of the instant amendment for the following reasons. The specification states on page 39, lines 1-3 that the use of the 6B5 and 2C7 antibodies together provide a means of enumerating

both cell populations (columnar and squamous). The specification describes the 2C7 antibody on pages 37-39 as specifically binding columnar epithelial cells, but that adenocarcinomas are also reactive to said antibody (page 38, lines 14-15). Thus, the 2C7 antibody does not fulfill the limitation of decreased percentage binding in neoplastic disease. On page 33, line 27 to page 34 line 1, the specification describes the reactivity of the 6B5 antibody, which binds to parabasal and basal cells in the columnar epithelium. However, the specification teaches that the 6B5 reactivity increases significantly in pathological conditions (page 34, lines 8-9) including CIN , lines 13-17 and carcinomas (lines 8-12). Thus, the 6B5 antibody does not exhibit the claimed property of decreased reactivity to pre-malignant or neoplastic cervical cells and the teachings of the specification regarding the combination of the 6B5 antibody with the 2C7 antibody does not support the amendment limitation requiring an antibody which specifically react with squamous cells and an antibody which specifically react with columnar cells.

The specification teaches on page 42, lines 16-19 that the 9G5 and the HG3 antibodies should be used in tandem. The specification teaches on page 40 (lines 21-28) that both antibodies react primarily on the superficial and intermediate squamous epithelium with normal cervical epithelium and that the HG3 antibody shows weak reactivity with columnar cells (page 41, lines 8-9). The specification teaches that both antibodies show decreased binding in CIN (page 41, lines 17-23) but that the HG3 antibody exhibited moderate to extensive reactivity to some squamous cell carcinomas (page 42, lines 3-4). Thus, the teaching of the specification regarding a method of using these antibodies in tandem do not support the instant claim amendment because the suggested combination of the 9G3 and HG3 antibodies do not include an antibody which specifically binds to columnar cells. The weak cross-reactivity of HG3 for columnar epithelial cells cannot be construed as "specifically binding" columnar epithelial cells, and the moderate and extensive reactivity to squamous cell carcinomas is not representative of a decrease in binding relative to normal cells.

It is noted that applicant has argued against the rejection under 102(b) as being anticipated by Porta et al by asserting (page 6, lines 18-20 of the response) that the instant claims are directed to screening for a premalignant or neoplastic disease state "in other words locating cellular changes which precede the development of the tumor". This statement is not found persuasive, as the term "neoplastic" encompasses both benign and malignant tumors. The

Declaration of C. Holmes which states that at the time of filing the term neoplastic was interchangeable with "premalignant" is also unpersuasive. It has been well known in the art that the term neoplastic encompasses both benign neoplasms and malignant neoplasms. This is evidenced by the abstract of Buchler et al (Archives of Gynecology, 1983, vol. 233 pp. 121-130) wherein cervical neoplasms are characterized as benign or malignant. Further, the "On-Line Medline Thesaurus of the National Library of Medicine" defines neoplastic as encompassing both malignant and benign neoplasms (see attachment). Thus the instant claims are drawn to methods of screening for premalignant and malignant neoplasms. However, the properties reported for said disclosed antibodies are not consistent with a decrease in binding in malignant neoplasms. Further, antibody 6B5 exhibited and increase in binding to non-malignant CIN.

Claim 3 is rejected for new matter for incorporating the limitation of "wherein the percentage binding of the two or more monoclonal antibodies to premalignant or neoplastic cells is decreased with respect to normal cells", for the reasons of record stated above. The specification teaches only two combinations of antibodies 6B5 with 2C7 and 9G5 with HG3. The 6B5 antibody shows increased reactivity to CIN and carcinomas, and the 2C7 antibody reacts with some carcinomas. The 9G5 and HG3 antibodies both show decreased reactivity to CIN, but the HG3 antibody strongly reacts with carcinomas. Thus, the specification does not provide support for this claim limitation.

Further, the suggestion by the specification that the 6B5 antibody be used in combination with the 2C7 antibody , and the 9G5 antibody be used in tandem with the HG3 antibody does not provide sufficient support for an amendment encompassing a genus of antibodies beyond those of the disclosed antibodies, even if either set of the claimed antibodies had the claimed characteristics, because the specification as filed teaches only the exact combinations of 6B5 and 2C7, and 9G5 and HG3 and does not contemplate a genus of antibodies having the claimed characteristics.

(B)As drawn to lacking written description

Claim 11 embodies the method of claim 1 wherein the surface antigens bound by said panel of monoclonal antibodies are not cytokeratins. The method is dependent upon a genus of surface antigens which are not cytokeratins. The specification states on page 27, lines 19-24 that with the exception of the 9G5 antibody, the molecular weight of the target antigens preclude

them from belonging to the cytokeratin family, and that a pan-cytokeratin antibody was used to establish that the 9G5 antibody did not bind to a cytokeratin. The specification does not further identify the target antigens. When given the broadest reasonable interpretation, claim 5 is a method claim dependent upon a genus of antibodies which bind surface antigens in normal cervical cells wherein the percentage binding of said antibodies is decreased in neoplastic and pre-malignant disease states. The genus of surface antigens encompassed by the method is large since only the down regulation or masking of the antigen in a pre-malignant or neoplastic state is required for members of the genus. The disclosure of the disclosed monoclonal antibodies 6B5, 2C7, 9G5, HG3 or BC4 fail to describe this genus because members of the genus include all antibodies which bind to surface proteins in cervical cells, wherein said surface proteins are downregulated or masked in a premalignant or malignant state. The specification fails to provide a description of how the antigens which are bound by the disclosed antibodies relate to the genus of surface proteins which are down regulated or masked in a pre-malignant or neoplastic disease state. One of skill in the art would reasonably conclude that applicant did not disclose a representative number of species to describe the genus of cell surface antigens encompassed by the instant method claims. Thus, the specification lacks adequate written description for claim 11.

8. The rejection of claims 1 and 2 under 35 U.S.C. as being unpatentable over Smedts et al is maintained. Applicant argues that Smedts does not render obvious the claimed invention as the samples used by Smedts are biopsy samples rather than cervical smears, and that the cellular material represented would differ from a cervical smear in that in the smear the more superficial layers of squamous cells are more highly represented. This has been considered but not found persuasive. It is noted that in Table 1 of Smedts , the reactivities of the various antibodies iare broken down into superficial, intermediate, parabasal and basal cells. Superficial cells having a reactivity to a specific antibody in a biopsy sample would have the same reactivity to exfoliated superficial cells in a cervical smear. Applicant further argues that in Figure 1 of Smedts et al only the antibody directed toward keratin 7 reliably binds to columnar cells in all women and that this antibody also show reactivity in squamous cells in CIN which would give rise to a false positive result. This has been considered but not found persuasive. It is noted that claim 1 does

not contain a limitation regarding the binding of the antibody which specifically binds columnar cells in relation to the premalignant or neoplastic cells. Further it is noted that there is no reactivity to keratin 7 in the superfical cells of neoplastic diseases of CIN I and II, which would fulfill the specific embodiment of a decrease in reactivity with respect to a normal sample. With regard to the new limitation that the antibody to squamous cells must show decreased binding to premalignant or neoplastic cells, it is noted that the antibody which is reactive to cytokeratin 13 reacts only with the ectocervical epithelium, which is consistent with the squamous epithelium, and shows a decrease in reactivity toward the neoplastic CIN III which is the same as that claimed. Further, the reactivity to those cell types is in the superficial layer which would be represented on a cervical smear of exfoliated cells.

9. It is recommended that applicant reduce the scope of the claims to the antibodies secreted by the deposited hybridomas, and methods of using the antibodies secreted by the deposited hybridomas in screening for CIN in cervical smears, rather than screening for premalignant or neoplastic diseases of the cervix.

10. Claims 5 and 7 are allowed.

11. All other rejections and objections as set forth in Paper no. 21 are withdrawn

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
9/5/2003